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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No.: 35

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Application Number: 08/286,189
Filing Date: 05 August, 1994
Appellants: Sanhueza, S. E., *et al.*

Michael I. Stewart
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 28 February, 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is inaccurate. Claims 1, 3-9, and 11-16 are pending in the instant application.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims stand or fall together and provides reasons as set forth in 37 C.F.R. 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

- Hall, C. B., 1994, "Prospects for a respiratory syncytial virus vaccine", Science, 265:1393-1394.
- Tristam, D. A., and R. C. Welliver, 1993, "Respiratory syncytial virus vaccines: can we improve on nature?", Pediatric Annals, 22:715-718.
- Toms, G. L., 1995, "Respiratory syncytial virus- how soon will we have a vaccine?", Arch. Dis. Child. 72:1-3.
- Murphy, B. R., *et al.*, 1994, "An update on approaches to the development of respiratory syncytial virus (RSV) and parinfluenza virus type 3 (PIV3) vaccines", Vir. Res. 32:13-36.
- Salkind, A. R., and N. J. Roberts, Jr., 1992, "Recent observations regarding the pathogenesis of recurrent respiratory syncytial virus infections: implications for vaccine development", Vaccine 10(8):519-523.

(10) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims:

35 U.S.C. § 112, First Paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-9, and 11-16 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward RSV vaccine compositions that are capable of inducing non-immunopotentiating and protective immune responses in humans, their methods of preparation, and immunization methods employing said vaccine compositions. The disclosure describes the preparation of a putative vaccine composition comprising purified and inactivated respiratory syncytial viruses (RSVs) of the subtype A (e.g., Long and A2 strains). Virus was prepared from infected vaccine quality VERO cells, concentrated by ultracentrifugation, purified by sucrose density gradient centrifugation, gel filtration, and chromatography, and inactivated by n-octyl-β-D-glucopyranoside (OG), β-propioloactone, or ascorbic acid treatment. These compositions were used to immunize cotton rats and their immunogenicity and pathogenicity examined. It was concluded by applicants (see p. 19) that inactivated RSV preparations elicited protective immune responses in the cotton rat without causing the exacerbated pulmonary pathology associated with other putative vaccine compositions. The specification does not provide any data from art-recognized primate models or from preliminary clinical studies.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that

several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows: **1) The disclosure fails to provide sufficient guidance pertaining to the correlates and determinants of protective immunity.** In order to develop an efficacious human RSV vaccine the skilled artisan would require a knowledge of those immune responses (i.e., humoral, cell-mediated, or both) that are critical for conferring protection against viral infection. The skilled artisan would also require a knowledge of the determinants modulating such immune responses so the proper immunogenic compositions can be prepared. However, **the art teaches that correlates and determinants of human protection remain to be elucidated** (Hall *et al.*, 1994; Toms, 1995). As Hall and colleagues note (see p. 1394, left col., second paragraph), **important hurdles remain pertaining to the development of an efficacious vaccine, the most important of which appears to be "the uncertainty about which components would constitute the ideal vaccine-live virus, attenuated virus, or purified viral proteins?"** The authors further emphasize (see p. 1394, middle col., first paragraph) that "**We do not even know what type of immune response would be safe and protective in young infants.**" Toms also points out (see p. 1, first paragraph) that "**Neither formalin inactivated nor live virus vaccines, administered intramuscularly, provided significant protection of infants and**

both have been associated with enhanced rather than reduced severity of disease on subsequent natural infection." Applicants are reminded that the disclosure fails to teach which RSV antigens and immunogenic compositions (i.e., live virus, inactivated virus, or subunit) can reasonably be expected to confer protective and non-immunopotentiating immune responses in humans.

2) The disclosure fails to provide suitable working embodiments. It is noted that applicants have administered their vaccine compositions to cotton rats. However, the claims encompass vaccine compositions, their methods of preparation, and methods of immunization employing said compositions, that confer protective and non-immunopotentiating responses in humans. Since the skilled artisan cannot make direct extrapolations, as it pertains to the immunoprotective and immunopotentiating nature of any given putative vaccine composition, between human and cotton rat animal systems (see point three below), the examples provided in the specification do not constitute proper working examples.

3) The disclosure fails to provide data from an art-recognized animal model. The art teaches that a suitable RSV vaccine animal model that enables the direct extrapolation of results obtained from *in vivo* studies to the clinic has not been developed (Hall, 1994; Toms, 1995; Murphy *et al.*, 1994). Hall concludes (see p. 1394, middle col., first paragraph) that "**Currently there is no accurate way to predict the response of infants to a candidate vaccine before actual administration."** Murphy and colleagues question the utility of the cotton rat model and note (see pp. 16 and 17, bridging paragraph) that "**the extent of RSV replication in cotton rats is much less than that in humans, and, consequently, the magnitude of immunopathological reactions would be expected to be more limited in scope"**. The authors also reported (see p. 17,

first and second paragraphs) that **immunogenic compositions with favorable characteristics in murine systems often fail in primate systems because of reduced immunogenicity, among other factors.** Toms also adds (see p. 2, right col., last paragraph) that the "**Protection of animals in the laboratory is much more easily achieved than protection of infants against natural infection.**" Thus, the skilled artisan, upon perusal of the art, would reasonably conclude that the cotton rat model does not represent a reasonable system for assessing the efficacy of a putative human RSV vaccine.

4) The art teaches that the development of efficacious human RSV vaccines is a difficult undertaking and has largely been unsuccessful (Salkind and Roberts, 1992; Tristam *et al.*, 1993; Hall, 1994; Murphy *et al.*, 1994; Toms, 1995). **A number of factors have contributed to vaccine failure including, *inter alia*, a lack of understanding of the correlates of human protection, antibody-mediated immune suppression in pediatric populations, the requirement for multiple immunizations, the quasispecies nature of RSV thereby necessitating broadly protective compositions, a lack of understanding of the mechanisms responsible for the pathological immunopotentiating effects observed with earlier vaccine candidates, and the lack of a suitable animal model.** The disclosure is silent pertaining to many of these considerations. Salkind and colleague appropriately add (see p. 521) that "**Despite intensive efforts, an effective vaccine for RSV has not been developed. The proper components of the vaccine have not been defined** but should probably include both RSV subgroups or shared determinants, and the components should induce serological, cellular, and especially mucosal immunity." Accordingly, when all

of the aforementioned factors have been considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

(11) Response to Argument

Applicants' traversal is based upon the assertion that the cotton rat model is reasonably predictive of vaccine efficacy in humans. Applicants assert that Coe *et al.* (1996) demonstrates that the cotton rat model is an art-recognized model of vaccine efficacy. This article references a publication by Groothuis *et al.* (19993) which applicants contend provides further evidence that the claimed invention is fully enabled. An unexecuted declaration, filed pursuant to 37 C.F.R. § 1.132, was provided by Dr. Gregory A. Prince. Applicants were advised in the accompanying advisory action that this declaration was not entered and not considered. Nevertheless, the purpose of this submission was to assert that anti-RSV immunoglobulin is capable of protecting against RSV disease. It was also asserted that neutralizing antibody titers of 1:350 or greater, as demonstrated in the cotton rat model, are protective. Applicants suggest that since the cotton rat model is an art-recognized animal model, the NIH allowed passive anti-RSV IgG prophylactic studies to proceed as reported in Groothuis *et al.* (19993). These arguments are not deemed to be persuasive.

First, the teachings of Coe *et al.* (1996) fail to establish the predictive value of employing the cotton rat model in assessing vaccine efficacy in humans. While this model is useful for studying certain respiratory infections, contrary to applicants' assertion, it is not predictive of vaccine efficacy in humans. The authors themselves reported that the "use of the model is hampered by a lack of immunological reagents and an incomplete knowledge of

the immune system of the cotton rat" (p. 323, rt. col.). There are numerous immunological and physiological differences between rats and humans. For instance, considering the MHC genotypic and phenotypic differences that exist between the two species, the skilled artisan would not reasonably expect the same viral antigen to be processed identically and induce the same immune response. This is because the cell surface MHC molecules on humans and rats will recognize different viral epitopes leading to different immune responses. A protective epitope in rats may not be recognized in humans and vice versa. Applicants are directed toward the teachings of Murphy *et al.* (1994) who clearly reported (see pp. 17, 21, and 22) that many immunogenic compositions in murine models fail to display the requisite immunogenicity in chimpanzees and humans. Thus, the observation that a certain titer of neutralizing antisera has been achieved *in vivo* in the cotton rat would not necessarily lead the skilled artisan to conclude that similar responses could be obtained in the clinic. Considerable genotypic differences exist between murine and primate hosts that influence, in an unpredictable manner, antigen processing and presentation. This is consistent with the evidence provided by Murphy and colleagues who note that several candidate vaccine compositions that induced high titers of neutralizing antibodies in murine systems **did not** display similar properties in primate models. Moreover, the teaching relied upon simply characterized the IgG isotype response in cotton rats in response to RSV infection. It did not address any of the caveats listed in the rejection pertaining to the correlates of protective immunity.

Second, the teachings of Groothuis *et al.* (1993) fail to address any of the defects noted *supra* in paragraph 10. This teaching was directed toward the prophylactic administration of RSV

immunoglobulin to high-risk infants. This study reported that high-titer anti-RSV Ig (titers ranged from 1:2400 to 1:8073, see left col., Study Design, p. 1525) was useful in passive transfer studies to prevent lower respiratory tract infection by RSV. This study was not directed toward vaccine efficacy, but passive transfer antibody studies. Thus, this study does not address any of the caveats discussed *supra* in paragraph 10. This study fails to identify suitable protective immunogens or epitopes. This study fails to demonstrate that the administration of the claimed vaccine would result in the development of a high-titer neutralizing antibody response in humans. The antibody samples employed in this study were highly concentrated. However, given the state of the prior art particularly as it applies to the lack of understanding pertaining to suitable protective immunogens and the lack of understanding pertaining to suitable protective immune responses, it seems extremely unlikely that the claimed vaccine composition would be capable of inducing suitable levels of antibodies in humans. Moreover, the applicants have no knowledge of the specificity and nature of the humoral immune response required for immunoprotection. Thus, based upon this teaching, the skilled artisan can not reasonably predict if any given RSV immunogen will confer protection in humans.

Third, as previously set forth, the prior art clearly provides a reasonable basis for questioning the validity of the cotton rat model and also epitomizes the difficulties associated with RSV vaccine development. Salkind and Roberts (1992) report that "vaccine development for RSV has been hampered by the inability of candidate vaccines to induce protective immunity to naturally occurring infection" (see p. 519, abstract). The authors also concluded (see p. 521) that "Despite intensive efforts, an effective vaccine for RSV has not been developed. The proper

components of the vaccine have not been defined ..." It was also noted that only incomplete protection could be obtained from RSV in immunized volunteers even in the presence of virus-specific antibody. Tristram and Welliver (1993) also reviewed the problems associated with RSV vaccine development and reported (see rt. col. p. 716) that "Perhaps the major difficulty in developing an RSV vaccine is the fact that natural infection confers only temporary, if any, protection against infection ... These findings raise the question of whether a vaccine actually could provide protection against infection." Hall (1994) provides a detailed review of the caveats pertaining to RSV vaccine development as follows (see p. 1394):

> What are the prospects for the development of a successful RSV vaccine? **Important hurdles remain. Perhaps most important is the uncertainty about which components would constitute the ideal vaccine--live virus, attenuated virus, or purified viral proteins?** The F and G glycoproteins appear pivotal in initiating immunity. However, **young infants respond poorly to heavily glycosylated proteins** (4). **Infants also have a diminished ability to produce protective neutralizing antibody to RSV in serum and respiratory secretions** (4, 6). In addition, **maternal antibody, which is uniformly present at the early age when vaccine would have to be administered, can have a dampening effect on the infant's immune response** (4).
>
> **Currently, there is no accurate way to predict the response of infants to a candidate vaccine before actual administration.** Are there measurable parameters that correlate with an immune response that is protective, durable, or detrimental? **We do not even know what type of immune response would be safe and protective in young infants.** Evidence has accumulated that certain serum antibodies are beneficial and protective, but they are only one part of the collage of RSV immunity, **as indicated by the virus's ability to infect some infants with high titers of maternal antibody** (3) ... we do not know whether the disease we see in infants is due to the replicating virus itself or to a cascade of inflammatory mediators it provokes.

The general problems facing RSV vaccine development were further addressed by Murphy *et al.* (1994). The authors summarized their findings and noted that a successful RSV vaccine will need to have several properties including an effectiveness in the presence of maternally-acquired serum antibodies, the induction of a level of resistance comparable to wild-type, the induction of resistance to both subgroups A and B, and the lack of a potentiating immune response during subsequent natural infection. The authors also addressed many of the problems associated with the cotton rat model in attempting to predict vaccine efficacy in humans. It was reported (see p. 16) that "**the extent of RSV replication in cotton rats is much less than that in humans, and, consequently, the magnitude of immunopathological reactions would be expected to be more limited in scope ... It is important to indicate that the interpretation of findings in cotton rats is controversial**". The authors further add that many vaccines are poorly immunogenic in humans and state (p. 17) that "**protein antigens of human pathogens that are highly immunogenic in mice can have greatly reduced immunogenicity in chimpanzees or humans. The high immunogenicity of a vaccinia-F recombinant virus in rodents was not seen in chimpanzees**". It was further reported that even though some vaccine preparations did not enhance the pulmonary histopathology associated with previous vaccine formulations, nevertheless, these preparations were "weakly immunogenic and only marginally protective in the lung". Toms (1995) also reviews the various caveats associated with RSV vaccine development (see p. 2) and notes that "**Protection of animals in the laboratory is much more easily achieved than protection of infants against natural infection** ... The discovery that chimpanzees, and by implication

human beings, are more permissive to the virus and less able to respond to successfully to virus antigens than rodents may help to explain past failures ... **a further major difference between the laboratory and the nursery lies in the nature of the challenging virus. Infants are exposed to a population of viruses the antigenic heterogeneity of which we are only just beginning to perceive.** The game we are playing with respiratory syncytial virus is not yet over and antigenic heterogeneity may prove to be its ace in the hole." Thus, the skilled artisan, upon reviewing the complexities associated with RSV vaccine development (e.g., the lack of understanding of the correlates of protective immunity (specificity and titer of immune response required), the lack of understanding of protective immunogens and the form they should take, the failure of infants to respond to glycosylated viral proteins, the inability of infants to produce neutralizing antibodies, the presence of dampening maternal neutralizing antibodies in infants, the inability to predict vaccine efficacy from rodent animal models) would reasonably conclude that the claimed invention is not enabled.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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